Q/ Do novel oral anticoagulants safely prevent stroke in patients with nonvalvular A-fib?

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EVIDENCE-BASED ANSWER

A/ Yes. Dabigatran, rivaroxaban, and apixaban are safe and effective compared with warfarin for preventing stroke in patients with nonvalvular atrial fibrillation. These novel oral anticoagulants (NOACs) are noninferior in reducing the number of strokes and systemic emboli and in lowering all-cause mortality while not increasing major bleeding complications and hemorrhagic events (strength of recommendation: **A**, consistent meta-analyses of randomized controlled trials [RCTs]).

Evidence summary

A 2014 meta-analysis of 4 RCTs including 71,683 patients with nonvalvular atrial fibrillation evaluated the NOACs dabigatran, rivaroxaban, apixaban, and edoxaban, for efficacy and safety compared with warfarin.[1] The RCTs analyzed 42,411 patients receiving NOACs and 29,272 patients receiving warfarin. All trials were designed to show noninferiority. Selection criteria for RCTs included all phase 3 trials of available NOACs (edoxaban isn't available in the United States). Median follow-up was 1.8 to 2.8 years.

Pooled data demonstrated that NOACs were noninferior to warfarin in preventing stroke or systemic embolism (relative risk [RR]=0.81; 95% confidence interval [CI], 0.73-0.91; number needed to treat [NNT]=147). The main benefit was derived from the relatively large decrease in the rate of hemorrhagic stroke (RR=0.49; 95% CI, 0.38-0.64; NNT=97) compared with warfarin. All-cause mortality was lower with NOACs as well (RR=0.90; 95% CI, 0.85-0.95; NNT=128).

A significant increase in gastrointestinal bleeding occurred with NOACs compared with warfarin (RR=1.3; 95% CI, 1.1-1.6; number needed to harm=185), but NOACs were associated with a decrease in intracranial hemorrhage similar to the reduction in hemorrhagic stroke (RR=0.48; 95% CI, 0.39-0.59; NNT=132).

NOACs show no significant difference in bleeding complications vs warfarin

A 2013 meta-analysis of 5 RCTs including 51,895 patients with nonvalvular atrial fibrillation compared the efficacy and safety of the NOACs dabigatran, rivaroxaban, apixaban, and ximelagatran, with the efficacy and safety of warfarin.[2] This review included the 3 studies of dabigatran, rivaroxaban, and apixaban from the previously described review, as well as 2 trials of ximelagatran that were not included in the other review (presumably because ximelagatran was no longer available owing to liver toxicity). This review didn't include the study of edoxaban that was published after the search dates of the literature review.

All trials were designed to show noninferiority. Selection criteria included a study population of at least 3000 patients and use of intention-to-treat analysis. Only 3 of the trials were double-blinded, and 2 were open-label. Mean follow-up was 16 months; median was 24 months.

NOACs were noninferior to vitamin K antagonists in the rate of stroke or systemic embolism (RR=0.82; 95% CI, 0.69-0.98; NNT=200), the rate of death from any cause

(RR=0.91; 95% CI, 0.85-0.96; NNT=145), and the rate of hemorrhagic strokes (RR=0.51; 95% CI, 0.41-0.64). NOACs showed no significant difference in major bleeding compared with warfarin (RR=0.83; 95% CI, 0.69-1.0), and were noninferior for minor bleeding (RR=0.88; 95% CI, 0.80-0.97). There was no difference in ischemic stroke (RR=0.87; 95% CI, 0.75-1.06) and major noncerebral bleeding (RR=0.88; 95% CI, 0.73-1.08).

The ACCP weighs in

The American College of Chest Physicians' 2012 clinical practice guidelines for antithrombotic therapy for atrial fibrillation recommend dabigatran 150 mg twice daily rather than adjusted-dose warfarin therapy for patients with nonvalvular atrial fibrillation requiring thromboembolism prophylaxis (Grade 2B, weak recommendation based on RCTs with important limitations).[3] **JFP**

References

1. Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet.* 2014;383:955-962.
2. Dogliotti A, Paolasso E, Giugliano RP, et al. Novel oral anticoagulants in atrial fibrillation: a meta-analysis of large, randomized, controlled trials vs warfarin. *Clin Cardiol.* 2013;36:61-67.
3. You JJ, Singer DE, Howard PA, et al. Antithrombotic therapy for atrial fibrillation: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest.* 2012;141(2 Suppl):e531S-e575S.